

## Refine Search

### Search Results -

Terms	Documents
L15 and injectable	34

Database:

US Pre-Grant Publication Full-Text Database  
 US Patents Full-Text Database  
 US OCR Full-Text Database  
 EPO Abstracts Database  
 JPO Abstracts Database  
 Derwent World Patents Index  
 IBM Technical Disclosure Bulletins

Search:

L16





### Search History

DATE: Thursday, March 25, 2004    [Printable Copy](#)    [Create Case](#)

#### Set Name Query

side by side

#### Hit Count Set Name

result set

*DB=USPT; PLUR=YES; OP=OR*

<u>L16</u>	L15 and injectable	34	<u>L16</u>
<u>L15</u>	l10 and L14	897	<u>L15</u>
<u>L14</u>	ratio by weight and L13	933817	<u>L14</u>
<u>L13</u>	l9 and L12	162645	<u>L13</u>
<u>L12</u>	alpha calcium sulfate hemihydrate	589277	<u>L12</u>
<u>L11</u>	l9 and L10	515	<u>L11</u>
<u>L10</u>	bell.in.	5601	<u>L10</u>
<u>L9</u>	L8 and mesenchymal cells	440878	<u>L9</u>
<u>L8</u>	bone precursor and L7	68191	<u>L8</u>
<u>L7</u>	cement and L6	8050	<u>L7</u>
<u>L6</u>	l2 and L5	256060	<u>L6</u>
<u>L5</u>	l3 and L4	362939	<u>L5</u>
<u>L4</u>	monobasic calcium phosphate monohydrate	370601	<u>L4</u>
<u>L3</u>	calcium phosphate monobasic	362939	<u>L3</u>

<u>L2</u>	beta tricalcium phosphate	380386	<u>L2</u>
<u>L1</u>	5484596.pn.	1	<u>L1</u>

END OF SEARCH HISTORY

## Refine Search

### Search Results -

Terms	Documents
L10 and L14	897

Database:

US Pre-Grant Publication Full-Text Database  
 US Patents Full-Text Database  
 US OCR Full-Text Database  
 EPO Abstracts Database  
 JPO Abstracts Database  
 Derwent World Patents Index  
 IBM Technical Disclosure Bulletins

Search:

L15

Refine Search

Recall Text

Clear

Interrupt

### Search History

DATE: Thursday, March 25, 2004    [Printable Copy](#)    [Create Case](#)

**Set Name Query**

side by side

**Hit Count Set Name**

result set

*DB=USPT; PLUR=YES; OP=OR*

<u>L15</u>	110 and L14	897	<u>L15</u>
<u>L14</u>	ratio by weight and L13	933817	<u>L14</u>
<u>L13</u>	19 and L12	162645	<u>L13</u>
<u>L12</u>	alpha calcium sulfate hemihydrate	589277	<u>L12</u>
<u>L11</u>	19 and L10	515	<u>L11</u>
<u>L10</u>	bell.in.	5601	<u>L10</u>
<u>L9</u>	L8 and mesenchymal cells	440878	<u>L9</u>
<u>L8</u>	bone precursor and L7	68191	<u>L8</u>
<u>L7</u>	cement and L6	8050	<u>L7</u>
<u>L6</u>	12 and L5	256060	<u>L6</u>
<u>L5</u>	13 and L4	362939	<u>L5</u>
<u>L4</u>	monobasic calcium phosphate monohydrate	370601	<u>L4</u>
<u>L3</u>	calcium phosphate monobasic	362939	<u>L3</u>
<u>L2</u>	beta tricalcium phosphate	380386	<u>L2</u>

L1 5484596.pn.

1 L1

END OF SEARCH HISTORY

## Hit List

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**Search Results - Record(s) 1 through 10 of 34 returned.**

☐ 1. Document ID: US 6696074 B2

L16: Entry 1 of 34

File: USPT

Feb 24, 2004

US-PAT-NO: 6696074

DOCUMENT-IDENTIFIER: US 6696074 B2

TITLE: Processing fetal or neo-natal tissue to produce a scaffold for tissue engineering

DATE-ISSUED: February 24, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dai; Jianwu	Boston	MA		
<u>Bell</u> ; Eugene	Boston	MA		
Russakovsky; Vladimir	Boston	MA		

US-CL-CURRENT: 424/423; 424/93.7, 435/1.1, 435/177, 435/395

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachment	Claims	RMK	Draw D
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☐ 2. Document ID: US 6566086 B1

L16: Entry 2 of 34

File: USPT

May 20, 2003

US-PAT-NO: 6566086

DOCUMENT-IDENTIFIER: US 6566086 B1

TITLE: Diagnostic kit for detecting creatine levels

DATE-ISSUED: May 20, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Al Athel; Fahad Mohammed Saleh	Riyadh			SA
<u>Bell</u> ; Thomas W.	Reno	NV		
Khasanov; Alisher B.	Carlsbad	CA		
Kaddurah-Daouk; Rima	Belmont	MA		

US-CL-CURRENT: 435/17; 514/1, 514/14, 546/233, 546/26, 546/27, 546/63, 546/73

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMCC	Draw De
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☐ 3. Document ID: US 6545124 B1

L16: Entry 3 of 34

File: USPT

Apr 8, 2003

US-PAT-NO: 6545124

DOCUMENT-IDENTIFIER: US 6545124 B1

TITLE: Peptide linkers for covalent linking polypeptide cell modulators

DATE-ISSUED: April 8, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Leslie David	Thame			GB
McCullagh; Keith Graham	Princes Risborough			GB
Porter; Alan George	High Wycombe			GB

US-CL-CURRENT: 530/326; 530/300, 530/387.1, 530/387.3

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMCC	Draw De
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☐ 4. Document ID: US 6441017 B1

L16: Entry 4 of 34

File: USPT

Aug 27, 2002

US-PAT-NO: 6441017

DOCUMENT-IDENTIFIER: US 6441017 B1

TITLE: Inhibitors of prenyl-protein transferase

DATE-ISSUED: August 27, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Ian M.	Harleysville	PA		
Beshore; Douglas C.	Lansdale	PA		
Gallicchio; Steven N.	Ambler	PA		
Zartman; C. Blair	Hatfield	PA		

US-CL-CURRENT: 514/393; 540/456, 540/472

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMCC	Draw De
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☐ 5. Document ID: US 6410534 B1

L16: Entry 5 of 34

File: USPT

Jun 25, 2002

US-PAT-NO: 6410534  
DOCUMENT-IDENTIFIER: US 6410534 B1

TITLE: Inhibitors of prenyl-protein transferase

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dinsmore; Christopher J.	Schwenksville	PA		
<u>Bell</u> ; Ian M.	Harleyville	PA		
Beshore; Douglas C.	Lansdale	PA		
Williams; Theresa M.	Harleysville	PA		

US-CL-CURRENT: 514/249; 514/250, 540/457, 540/458, 540/459, 540/461, 540/468,  
540/469, 540/471, 540/472, 540/476, 540/477

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMC	Draw Da
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☐ 6. Document ID: US 6358985 B1

L16: Entry 6 of 34

File: USPT

Mar 19, 2002

US-PAT-NO: 6358985  
DOCUMENT-IDENTIFIER: US 6358985 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: Inhibitors of prenyl-protein transferase

DATE-ISSUED: March 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Anthony; Neville J.	Hatfield	PA		
<u>Bell</u> ; Ian M.	Harleysville	PA		
Beshore; Douglas C.	Lansdale	PA		
Ciccarone; Terrence M.	Telford	PA		
de Solms; S. Jane	Norristown	PA		
Dinsmore; Christopher J.	Schwenksville	PA		
Stokker; Gerald E.	Gwynedd Valley	PA		

US-CL-CURRENT: 514/393; 540/455, 540/456, 540/468

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMC	Draw Da
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☐ 7. Document ID: US 6265581 B1

L16: Entry 7 of 34

File: USPT

Jul 24, 2001

US-PAT-NO: 6265581

h e b b g e e f e ef b c

DOCUMENT-IDENTIFIER: US 6265581 B1

TITLE: Selective .beta.3 adrenergic agonists

DATE-ISSUED: July 24, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Michael Gregory	Indianapolis	IN		
Crowell; Thomas Alan	Indianapolis	IN		
Droste; Christine Ann	Indianapolis	IN		
Jesudason; Cynthia Darshini	Indianapolis	IN		
Matthews; Donald Paul	Indianapolis	IN		
McDonald, III; John Hampton	Carmel	IN		
Neel; David Andrew	Zionsville	IN		
Rito; Christopher John	Mooresville	IN		
Shuker; Anthony John	Indianapolis	IN		
Winter; Mark Alan	Indianapolis	IN		

US-CL-CURRENT: 546/277.4; 546/273.7, 548/491

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMC	Drawings
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☐ 8. Document ID: US 6235481 B1

L16: Entry 8 of 34

File: USPT

May 22, 2001

US-PAT-NO: 6235481

DOCUMENT-IDENTIFIER: US 6235481 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: Polynucleotides encoding calpain 10

DATE-ISSUED: May 22, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Horikawa; Yukio	Kobe			JP
Oda; Naohisa	Nagoya			JP
Hanis; Craig L.	Houston	TX		
<u>Bell</u> ; Graeme I.	Chicago	IL		
Cox; Nancy J.	Inverness	IL		

US-CL-CURRENT: 435/6; 536/23.1, 536/24.1

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMC	Drawings
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☐ 9. Document ID: US 6187533 B1



L16: Entry 9 of 34

File: USPT

Feb 13, 2001

US-PAT-NO: 6187533

DOCUMENT-IDENTIFIER: US 6187533 B1

**\*\* See image for Certificate of Correction \*\***TITLE: Mutations in the diabetes susceptibility genes hepatocyte nuclear factor (HNF) 1 alpha (.alpha.), HNF1.beta. and HNF4.alpha.

DATE-ISSUED: February 13, 2001

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Graeme I.	Chicago	IL		
Yamagata; Kazuya	Kaizuka			JP
Oda; Naohisha	Chicago	IL		
Kaisaki; Pamela J.	Headington			GB
Furuta; Hiroto	Wakayama			JP
Horikawa; Yukio	Chicago	IL		
Menzel; Stephan	Headington			GB

US-CL-CURRENT: 435/6; 435/91.2

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMOC	Drawings
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☐ 10. Document ID: US 6133458 A

L16: Entry 10 of 34

File: USPT

Oct 17, 2000

US-PAT-NO: 6133458

DOCUMENT-IDENTIFIER: US 6133458 A

TITLE: Benzo[B]indeno[2, 1-D]thiophene compounds, intermediates, compositions, and methods

DATE-ISSUED: October 17, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Michael Gregory	Indianapolis	IN		
Muehl; Brian Stephen	Indianapolis	IN		
Winter; Mark Alan	Indianapolis	IN		

US-CL-CURRENT: 549/42

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KMOC	Drawings
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Terms	Documents
L15 and injectable	34

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**Search Results - Record(s) 11 through 20 of 34 returned.**☐ 11. Document ID: US 6130333 A

L16: Entry 11 of 34

File: USPT

Oct 10, 2000

US-PAT-NO: 6130333

DOCUMENT-IDENTIFIER: US 6130333 A

**\*\* See image for Certificate of Correction \*\***TITLE: Bicyclic imidazolyl derivatives as phosphodiesterase inhibitors,  
pharmaceutical compositions and method of use

DATE-ISSUED: October 10, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huang; Horng-Chih	Chesterfield	MO		
Chamberlain; Timothy S.	Des Plaines	IL		
Settle; Steven Lynn	Wildwood	MO		
Joy; William Dean	Creve Coeur	MO		
Siegel; Ned R.	Belleville	IL		
Bell; Leslie D.	Chesterfield	MO		

US-CL-CURRENT: 546/118; 546/273.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWD	Draw Ds
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☐ 12. Document ID: US 6093735 A

L16: Entry 12 of 34

File: USPT

Jul 25, 2000

US-PAT-NO: 6093735

DOCUMENT-IDENTIFIER: US 6093735 A

TITLE: Selective .beta.-3 adrenergic agonists

DATE-ISSUED: July 25, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bell; Michael Gregory	Indianapolis	IN		
Crowell; Thomas Alan	Indianapolis	IN		

Droste; Christine Ann	Indianapolis	IN
Jesudason; Cynthia Darshini	Indianapolis	IN
Matthews; Donald Paul	Indianapolis	IN
McDonald, III; John Hampton	Carmel	IN
Neel; David Andrew	Zionsville	IN
Rito; Christopher John	Mooresville	IN
Shuker; Anthony John	Indianapolis	IN
Winter; Mark Alan	Indianapolis	IN

US-CL-CURRENT: [514/338](#); [514/344](#), [514/355](#), [514/359](#), [514/415](#)

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	KIMC	Draw D
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☐ 13. Document ID: US 6075040 A

L16: Entry 13 of 34

File: USPT

Jun 13, 2000

US-PAT-NO: 6075040

DOCUMENT-IDENTIFIER: US 6075040 A

TITLE: Selective .beta..sub.3 adrenergic agonists

DATE-ISSUED: June 13, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bell; Michael Gregory	Indianapolis	IN		
Crowell; Thomas Alan	Indianapolis	IN		
Jesudason; Cynthia Darshini	Indianapolis	IN		
Matthews; Donald Paul	Indianapolis	IN		
McDonald, III; John Hampton	Carmel	IN		
Neel; David Andrew	Zionsville	IN		
Rito; Christopher John	Mooresville	IN		
Shuker; Anthony John	Indianapolis	IN		
Winter; Mark Alan	Indianapolis	IN		

US-CL-CURRENT: [514/362](#); [514/395](#), [548/126](#), [548/304.7](#), [548/306.7](#)

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequence	Attachments	Claims	KIMC	Draw D
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☐ 14. Document ID: US 6060492 A

L16: Entry 14 of 34

File: USPT

May 9, 2000

US-PAT-NO: 6060492

DOCUMENT-IDENTIFIER: US 6060492 A

TITLE: Selective .beta.3 adrenergic agonists

DATE-ISSUED: May 9, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bell; Michael Gregory	Indianapolis	IN		
Crowell; Thomas Alan	Indianapolis	IN		
Matthews; Donald Paul	Indianapolis	IN		
McDonald, III; John Hampton	Carmel	IN		
Neel; David Andrew	Zionsville	IN		
Shuker; Anthony John	Indianapolis	IN		
Winter; Mark Alan	Indianapolis	IN		

US-CL-CURRENT: 514/359; 514/234.5, 514/241, 514/254.06, 514/338, 514/362, 514/376, 514/381, 514/386, 514/387, 514/415, 544/139, 544/219, 544/237, 546/273.7, 548/134, 548/221, 548/253, 548/261, 548/304.7, 548/306.4, 548/503

Full	Title	Citation	Front	Review	Classification	Date	Reference	Deposited	Attachments	Claims	KWMC	Draw. De
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☐ 15. Document ID: US 6013648 A

L16: Entry 15 of 34

File: USPT

Jan 11, 2000

US-PAT-NO: 6013648

DOCUMENT-IDENTIFIER: US 6013648 A

TITLE: CB.sub.2 Receptor agonist compounds

DATE-ISSUED: January 11, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rinaldi; Murielle	Saint Georges d'Orques			FR
Barth; Francis	Montpellier			FR
Casellas; Pierre	Montpellier			FR
Congy; Christian	Saint Gely du Fesc			FR
Oustric; Didier	Le Cres			FR
Bell; Malcolm R.	East Greenbusch	NY		
D'Ambra; Thomas E.	Rexford	NY		
Phillion; Richard E.	Pottstown	PA		

US-CL-CURRENT: 514/235.2; 514/228.2, 514/323, 514/414, 514/419, 544/143, 544/144, 544/58.5, 546/201, 548/465, 548/468, 548/493

Full	Title	Citation	Front	Review	Classification	Date	Reference	Deposited	Attachments	Claims	KWMC	Draw. De
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☐ 16. Document ID: US 5977154 A

L16: Entry 16 of 34

File: USPT

Nov 2, 1999

US-PAT-NO: 5977154

DOCUMENT-IDENTIFIER: US 5977154 A

TITLE: Selective .beta.3 adrenergic agonist

DATE-ISSUED: November 2, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Michael Gregory	Indianapolis	IN		
Droste; Christine Ann	Indianapolis	IN		
Jesudason; Cynthia Darshini	Indianapolis	IN		
Rito; Christopher John	Mooresville	IN		
Shuker; Anthony John	Indianapolis	IN		
Winter; Mark Alan	Indianapolis	IN		

US-CL-CURRENT: 514/394; 514/234.5, 514/253.09, 514/254.06, 514/254.09, 514/318,  
514/322, 514/359, 514/406, 514/414, 514/415, 544/124, 544/132, 544/139, 544/140,  
544/144, 544/364, 544/366, 544/370, 544/371, 544/373, 546/194, 546/199, 546/268.4,  
546/273.4, 546/275.7, 546/277.4

Full	Title	Citation	Front	Review	Classification	Date	Reference	Examiner's	Attachments	Claims	KWIC	Draw De
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☐ 17. Document ID: US 5939443 A

L16: Entry 17 of 34

File: USPT

Aug 17, 1999

US-PAT-NO: 5939443

DOCUMENT-IDENTIFIER: US 5939443 A

TITLE: Selective .beta.3 adrenergic agonists

DATE-ISSUED: August 17, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Michael Gregory	Indianapolis	IN		
Crowell; Thomas Alan	Indianapolis	IN		
Droste; Christine Ann	Indianapolis	IN		
Matthews; Donald Paul	Indianapolis	IN		
McDonald, III; John Hampton	Carmel	IN		
Rito; Christopher John	Mooresville	IN		
Shuker; Anthony John	Indianapolis	IN		
Winter; Mark Alan	Indianapolis	IN		

US-CL-CURRENT: 514/359; 514/234.5, 514/241, 514/254.06, 514/338, 514/362, 514/376,  
514/381, 514/386, 514/387, 514/415, 544/139, 544/219, 544/237, 546/273.7, 548/134,  
548/221, 548/253, 548/261, 548/304.7, 548/306.4, 548/503

Full	Title	Citation	Front	Review	Classification	Date	Reference	Examiner's	Attachments	Claims	KWIC	Draw De
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☐ 18. Document ID: US 5939414 A

L16: Entry 18 of 34

File: USPT

Aug 17, 1999

US-PAT-NO: 5939414

DOCUMENT-IDENTIFIER: US 5939414 A

TITLE: Benzodiazepine hydrazide derivatives as inhibitors of HIV integrase

DATE-ISSUED: August 17, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Ian M.	Harleysville	PA		
Hazuda; Daria Jean	Lansdale	PA		
Guare, Jr.; James P.	Quakertown	PA		
Munson; Peter M.	Harleysville	PA		
Thompson; Wayne J.	Lansdale	PA		
Vacca; Joseph P.	Telford	PA		

US-CL-CURRENT: 514/221; 540/572

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KIMC	Draw. De
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☐ 19. Document ID: US 5856341 A

L16: Entry 19 of 34

File: USPT

Jan 5, 1999

US-PAT-NO: 5856341

DOCUMENT-IDENTIFIER: US 5856341 A

TITLE: Benzo [B] indeno [2,1-D] thiophene compounds, intermediates, processes, compositions and methods

DATE-ISSUED: January 5, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
<u>Bell</u> ; Michael Gregory	Indianapolis	IN		
Muehl; Brian Stephen	Indianapolis	IN		
Winter; Mark Alan	Indianapolis	IN		

US-CL-CURRENT: 514/324; 514/217.03, 514/232.8, 514/422, 514/443, 540/596, 544/145, 546/202, 548/527, 549/42

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KIMC	Draw. De
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☐ 20. Document ID: US 5840738 A

L16: Entry 20 of 34

File: USPT

Nov 24, 1998

US-PAT-NO: 5840738

DOCUMENT-IDENTIFIER: US 5840738 A

TITLE: Selective .beta.-3 adrenergic agonists

DATE-ISSUED: November 24, 1998

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bell; Michael Gregory	Indianapolis	IN		
Crowell; Thomas Alan	Indianapolis	IN		
Droste; Christine Ann	Indianapolis	IN		
Jesudason; Cynthia Darshini	Indianapolis	IN		
Matthews; Donald Paul	Indianapolis	IN		
McDonald, III; John Hampton	Carmel	IN		
Neel; David Andrew	Zionsville	IN		
Rito; Christopher John	Mooresville	IN		
Shuker; Anthony John	Indianapolis	IN		
Winter; Mark Alan	Indianapolis	IN		

US-CL-CURRENT: 514/359; 514/234.2, 514/234.5, 514/235.2, 514/248, 514/254.06,  
514/254.09, 514/322, 514/323, 514/394, 514/406, 514/414, 514/415, 544/132, 544/139,  
544/140, 544/144, 544/370, 544/371, 544/373, 546/199, 546/201, 548/259, 548/306.1,  
548/306.4, 548/307.1, 548/307.4, 548/309.7, 548/361.5, 548/362.1, 548/362.5 ,  
548/465, 548/483, 548/486, 548/503

Full	Title	Citation	Front	Review	Classification	Date	Reference	Abstracts	Attachments	Claims	KMIC	Draw Dg
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L5: Entry 1 of 1

File: USPT

Apr 6, 1999

DOCUMENT-IDENTIFIER: US 5891558 A

TITLE: Biopolymer foams for use in tissue repair and reconstruction

Brief Summary Text (16):

Orthopedic and dental implants can also be produced from the foam and foam compositions, with or without extracellular matrix particulates, of the invention. Typically, the foam and foam compositions which are used as orthopedic and dental implants include calcium phosphate cement. An example of such a dental implant is an alveolar ridge builder which is composed of a double density biopolymer foam in the form of a tube containing resorbable calcium phosphate cement. Alternatively, the biopolymer foams and foam compositions can be produced to include hydroxyapatite and used, for example, as dental implants. An alveolar ridge substitute which includes a double density biopolymer foam in the form of a tube containing nonresorbable hydroxyapatite is an example of such a dental implant.

Brief Summary Text (17):

Also contemplated herein are dental implants capable of promoting periodontal ligament repair and bone rebuilding and methods for promoting periodontal ligament repair and bone rebuilding using these implants. Typically, these dental implants include an apron shaped double or quadruple density biopolymer foam. In one embodiment, the apron shaped double or quadruple density biopolymer foam includes an outpocketing containing calcium phosphate cement. To promote periodontal ligament repair and bone rebuilding, an area of tooth requiring periodontal ligament repair and bone rebuilding is contacted with the apron shaped foam, e.g., by the tying the strings of the double or quadruple density biopolymer foam around a tooth to secure the apron to an area of tooth requiring periodontal ligament repair and bone rebuilding.

Brief Summary Text (18):

In yet another aspect, the biopolymer foams and foam compositions of the invention can be used as connective tissue implants, e.g., cartilage, tendon, ligament implants. In one embodiment, the foams and foam compositions are prepared as cartilage implants. In a preferred embodiment, the cartilage implants include a substrate including a biopolymer solution and a calcium phosphate cement which has set into a cement and a single or double density biopolymer foam embedded, e.g., by freeze-drying, in one face of the cementous substrate. The single or double density biopolymer foam of the cartilage implant can also be seeded with chondrocytes. In another embodiment, the foams and foam compositions are prepared as ligament implants. Typically, the ligament implants are composed of a plurality of biopolymer filaments and a single or double density biopolymer foam.

Brief Summary Text (32):

Biopolymer fabrics, e.g., nonwoven biopolymer fabrics, are typically composed of a mat of entangled biopolymer fibers of a selected size and density. Typically, the nonwoven biopolymer fabrics are produced by spooling dry biopolymer fiber onto a drum of circumference equal to that of the length of an individual fiber element. Spooling is continued until the number of wraps of fiber on the drum equals the number of pieces of fiber required for the fabric. A cut is then made across the

wound fiber in a direction parallel to the drum axis and the fibers are removed from the drum. The fiber can then be crosslinked if it has not been previously crosslinked. The fiber is then dispersed in a volume of a phosphate buffer solution for a period of time to decrease its pH and soften the fiber. The fiber is transferred to a volume of water and agitated mechanically to produce entanglement of the fiber strands. The entangled fiber strands are sieved from the water onto a collection screen until they coat the screen in a mat of uniform density. The mat is then dried on the screen or after transfer to another surface, screen, or cell culture device. If desired, the nonwoven mat can be cut or punched into smaller shapes after drying.

Brief Summary Text (41):

Growth factors necessary for cell growth are attached to structural elements of the extracellular matrix. The structural elements include proteins, e.g., collagen and elastin, glycoproteins, proteoglycans and glycosaminoglycans. The growth factors, originally produced and secreted by cells, bind to the extracellular matrix and regulate cell behavior in a number of ways. These factors include, but are not limited to, epidermal growth factor, fibroblast growth factor (basic and acidic), insulin-like growth factor, nerve growth-factor, mast cell-stimulating factor, the family of transforming growth factor .beta., platelet-derived growth factor, scatter factor, hepatocyte growth factor and Schwann cell growth factor. Adams et al., "Regulation of Development and Differentiation by the Extracellular Matrix" Development Vol. 117, p. 1183-1198 (1993) (hereinafter "Adams et al.") and Kreis et al. editors of the book entitled "Guidebook to the Extracellular Matrix and Adhesion Proteins," Oxford University Press (1993) (hereinafter "Kreis et al. ") describe extracellular matrix components that regulate differentiation and development. Further, Adams et al. disclose examples of association of growth factors with extracellular matrix proteins and that the extracellular matrix is an important part of the micro-environment and, in collaboration with growth factors, plays a central role in regulating differentiation and development. The teachings of Adams et al. and Kreis et al. are incorporated herein by reference.

Brief Summary Text (46):

The foams and foam compositions can also be used as prostheses which can be introduced or grafted into recipients, e.g., such as mammalian recipients, e.g., humans. For example, the foams and foam compositions can be used as a prosthesis or to reconstitute, for example, the following types of tissue: nervous tissue, skin, vascular tissue, muscle tissue, connective tissue such as bone, cartilage, tendon, and ligament, kidney tissue, liver tissue, and pancreatic tissue. Tissue cells seeded into these foams and foam compositions can be obtained from a mammal, e.g., a human. Tissue cells are delivered to the foams and foam compositions by first suspending the cells in small volumes of tissue culture medium. The tissue culture medium which contains the cells can then be applied in drops to the foams or foam compositions. Alternatively, the foams or foam compositions can be placed in a vessel which contains the tissue culture medium and cells in suspension and which shakes such that the tissue culture medium containing the cells is distributed throughout the foams and foam compositions. In another embodiment, tissue cells can be suspended in a biopolymer solution e.g., a collagen solution, at low concentrations, at a temperature of about 4.degree. C. to 10.degree. C., and at a pH of about 7.0. The solution containing the cells can then be delivered to the foams and foam compositions. As foam is warmed to 37.degree. C., the biopolymer solution, e.g., collagen solution, forms a gel in the foam. As used herein, the term "gel" refers a network or mesh or biopolymer filaments together with an aqueous solution trapped within the network or mesh of biopolymer filaments. An alginate gel for use as a delivery vehicle of cells to the foams or foam compositions of the invention can be produced by addition of calcium which causes polymerization at room temperature and at a neutral pH. Selected epithelial, endothelial, or mesothelial cells can then be plated onto the surface of the gel-filled foam or foam composition.

Brief Summary Text (51):

For rebuilding bone, cartilage, tendon, and ligament, the foams and foam compositions of the invention can be seeded with the appropriate cells, e.g., connective tissue cells such as osteocytes, chondrocytes, and tendon and ligament fibrocytes, and molded in the appropriate form to repair damaged connective tissue. In one embodiment, the biopolymer foams of the invention, with or without extracellular matrix particulates, can be mixed with calcium phosphate cement, e.g., .beta.-tricalcium phosphate cement which includes 64% .beta.-tricalcium phosphate, 16% calcium phosphate monobasic, 15% calcium sulfate hemihydrate, and 5% calcium pyrophosphate (see Mirtichi et al. (1989) Biomaterials 10:634-638) to produce a reinforced cement for use as, for example, orthopedic or dental implants. Gelatin, a derivative of collagen which constitutes much of the organic content of bone, can be added to the calcium phosphate cement as an adhesive. In another embodiment, the biopolymer foams of the invention are cast onto the cement and processed as described herein. Alternatively, the extracellular matrix particulates described herein can be mixed with calcium phosphate cement and used as orthopedic or dental implants. The biopolymer foams and/or extracellular matrix particulates increase bone cell invasion of the calcium phosphate cement. In addition, growth factors present in the extracellular matrix particulates provide mitogenic stimuli to increase the rate at which the bone cells multiply and replace the cement. For example, it has been found that extracellular matrix particulates from a variety of tissues, when added to culture inserts, stimulated mitosis in a variety of different cell types when compared to culture inserts without the extracellular matrix particulates. See Table 2 which shows the results of experiments in which 1 mg of extracellular matrix particulates from the indicated tissue origin were added to culture inserts containing the indicated cell types in serum-free medium. After five days, the cell number in the cultures containing the extracellular matrix particulates and the cell number in the control cultures without the extracellular matrix particulates was determined.

Brief Summary Text (52):

The biopolymer solutions, foams and/or extracellular matrix particulates as well as biopolymer fibers, e.g., braided fibers, and biopolymer fabrics can also increase the strength of the calcium phosphate-based cement by at least about 20%, at least about 30%, at least about 40%, and preferably at least about 50% or more if mixed with the cement in appropriate proportions. For example, when liquid collagen is added in the proportion of 5 mg of collagen to 8 g of cement or when extracellular matrix particulates are added in the proportion of 0.1 g extracellular matrix particulates to 8 g cement, the strength, as measured by pounds resisted until the cement breaks, of the cement increase 50% over that of cement without collagen or extracellular matrix particulates.

Brief Summary Text (53):

Cartilage implants are additional examples of implants which can be produced using the foams or foam compositions of the invention. In one embodiment, cartilage implants are generated by combining a biopolymer, e.g., collagen, solution with calcium phosphate cement and allowing the mixture to set (but not dry) into a cement. While the cement is still plastic and malleable, a biopolymer solution is cast onto the set but not dry cement and freeze-dried to form a layer of single or double density biopolymer foam embedded in one face of the cementous substrate. After the cement has set and dried, the biopolymer foam is seeded with chondrocytes. In an alternative embodiment, cartilage implants are produced by combining a biopolymer, e.g., collagen, solution with calcium phosphate cement and allowing the mixture to set and dry into a cement. The set and dry cement can then be rehydrated and saturated with biopolymer solution. A biopolymer solution can then be cast onto the cementous substrate and the assembly of the layer of biopolymer solution and the cementous substrate is freeze-dried to form a layer of single or double density biopolymer foam embedded in one face of the cementous substrate. The biopolymer foam can then be seeded with chondrocytes, e.g., human chondrocytes (e.g., at 5.times.10.sup.4 -4.times.10.sup.6 cells/ml of foam). In

either embodiment, the chondrocytes are allowed to differentiate and create a matrix typical of cartilage tissue and then are placed in an articulating relationship. Typically, an articulating relationship for the cartilage implant is established using a mechanical device for growing and developing particular cartilage. Such a mechanical device places the biopolymer foam containing the chondrocytes into gentle contact with a second surface, e.g., a second biopolymer foam containing chondrocytes, in the presence of fluid having similar characteristics as those of synovial fluid and which contains hyaluronic acid, e.g., a dialysate of blood plasma, such that it becomes a thixotropic fluid, i.e., a gel which liquefies when agitated but which reverts to a gel upon standing. The biopolymer foam containing the chondrocytes and the second surface are then rotated or slid across one another to create shear and compressive forces which mimic those to which cartilage tissue is exposed in vivo. The resulting cartilage tissue has the properties of normal articular cartilage tissue, e.g., the ability and architecture to withstand forces to which normal cartilage tissue is exposed.

Brief Summary Text (54):

Ligament implants, as multifilament forms of the biopolymers of the invention, can be enhanced with the foams and foam compositions of the invention to promote cell seeding. For example, continuous ligament multifilament structures can be produced with or without the addition of extracellular matrix particulates, to have selected characteristics. Ligament cells can then be delivered to the ligament which can be embedded in a foam casing. The ends of the ligament can be cut and embedded in calcium phosphate cement. The ligament can then be mounted in a tubular tissue maturation chamber. After the ligament cells have attached to the ligament, the ligament is subjected to a regime of cyclical axial elongation resulting in stress, which is increased in magnitude as the ligament matures. The mature biopolymer ligaments can be used, for example, as ligament prostheses.

Brief Summary Text (55):

Dental implants can be formed from the foams and foam compositions of the invention. For example, the foams and foam compositions can be prepared as specialized dental implants for periodontal ligament repair and bone rebuilding. In one embodiment, the foams and foam compositions of the invention are prepared as apron shaped implants which can be fixed to a tooth by tying the strings of the apron around the tooth. In another embodiment, the foams and foam compositions are designed as covers of post extraction sockets filled with calcium phosphate cement or collagen composition which is reinforced with calcium phosphate cement. In yet another embodiment, the foams and foam compositions are designed as calcium phosphate- or hydroxyapatite-filled tubes to serve as alveolar ridge builders.

Brief Summary Text (56):

The apron shaped foam, which can be produced as a double density or quadruple density foam, i.e., a double density foam folded over on itself, for promoting periodontal ligament repair and bone rebuilding can be positioned between a gum flap and the alveolar bone in the area requiring periodontal ligament repair and bone rebuilding. The foam can be designed to block invasion by junctional epithelium of the cleaned and planed tooth zone. Periodontal ligament cells can then migrate into the foam, bind to the foam, and secrete extracellular matrix products into the foam. The foam can also be invaded by capillary endothelial cells and immune cells which provide defense against microbial assault. By excluding epithelium and by stimulating periodontal ligament cells, the foam can promote regeneration of periodontal ligament and alveolar bone. The apron shaped dental implants can also be modified to include a calcium phosphate cement as described herein. In one embodiment, the calcium phosphate cement can be included in an outpocketing of the apron which can be placed on the eroded alveolar bone. The calcium phosphate cement provides pathways for invading bone cells and hardens when hydrated. The apron shaped dental implant can also include extracellular matrix particulates generated from dental tissues. These extracellular matrix particulates provide the appropriate growth factors, e.g., bone and ligament specific growth

factors, for promoting periodontal ligament cell and bone cell growth into the implant.

Brief Summary Text (57):

Alternatively, the foams and foam compositions of the invention can be prepared as post extraction socket fillers. The foams can be mixed with calcium phosphate cement and inserted into sockets of extracted teeth. These socket fillers promote bone regeneration within the socket which, at a minimum, provides a foundation for a metal, e.g., titanium, fixture and subsequent application of a crown. The titanium or other material fixture can be anchored in a socket immediately after an extraction with calcium phosphate cement reinforced with one of the foam or foam compositions described herein. The implant can then be covered or "tented" with a double or quadruple double density foam membrane described herein as an apron. The socket fillers can also include extracellular matrix particulates generated from bone tissue or dental papilla. These extracellular matrix particulates provide the appropriate growth factors, e.g., bone specific growth factors, for promoting bone cell growth into the implant. In addition, in instances where the bony foundation for dental implants composed of metal does not provide adequate support for the metal implant, calcium phosphate cement reinforced or strengthened with the foams and foam compositions of the invention can be used to reinforce the bony foundation.

Brief Summary Text (58):

In yet another embodiment, the foams and foam compositions can be designed as alveolar ridge substitutes or alveolar ridge builders. Alveolar ridge substitutes are used to provide underpinning for dentures. Typically, the alveolar ridge substitutes are designed as double density foam tubes of the appropriate length which are filled with non-resorbable hydroxyapatite (or with the calcium phosphate cement described herein) to build up a mineralized platform along the alveolar ridge and to promote development of bone and a connective tissue framework around the hydroxyapatite particles. The alveolar ridge builders of the invention have the same design as that of the alveolar ridge substitutes except that the foam tube is filled with calcium phosphate cement which promotes bone development but which is resorbable. The composition of the alveolar ridge builders promotes bone cell and blood capillary penetration leading to regrowth and restoration of the ridge prior to, for example, installation of a denture or a metal implant. The foam tube of the alveolar ridge builder can also include extracellular matrix particulates which promote alveolar ridge bone regeneration.